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(54) Title: AMINO ACID COMPOSITION FOR PARENTERAL NUTRITIONAL SUPPORT AND THE USE THEREOF

(57) Abstract

The invention relates to a composition for therapeutic, especially postoperative and posttraumatic, parenteral nutritional support treatment, which composition is based on a conventional amino acid mixture, the composition being characterised in that it also includes L-glutamine and/or alpha-ketoglutarate and optionally L-asparagine, the components of the composition, expressed in g dry component/l aqueous solution, being: glycine (1-12), aspartate (1-10), glutamate (2-12), alanine (2-20), arginine (2-14), cysteine/cystine (0.4-2.0), histidine (2-8), isoleucine (2-8), leucine (2-8), lysine (2-12), methionine (1-6), phenylalanine (4-10), proline (4-10), serine (2-10), threonine (2-8), tryptophan (1-3), tyrosine (0.2-1), valine (2-8), and additionally 5-30 g/l L-glutamine and/or 5-25 g/l alpha-ketoglutarate, and optionally 0.5-10 g/l L-asparagine and/or acetoacetate, or salts or esters thereof. The invention also relates to the use of L-glutamine and/or its derivative alpha-ketoglutarate, and optionally L-asparagine and/or its derivative acetoacetate for the preparation of a composition intended for therapeutic, especially postoperative and posttraumatic, parenteral nutritional support treatment, which use is characterised in that L-glutamine and/or alpha-ketoglutarate and optionally L-asparagine and/or acetoacetate, dissolved in water and sterile-filtered, are added in cold-stored and freeze dried form or other sterile powder form to a commercial amino acid nutrient solution immediately before the therapeutic treatment.

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Amino acid composition for parenteral nutritional support and the use thereof.

The present invention relates to a composition for therapeutic, especially postoperative and post-traumatic, parenteral nutritional support treatment, which composition, in addition to conventional amino acid components, also contains L-glutamine and/or its derivative alpha-ketoglutarate, and optionally L-asparagine and acetoacetate.

Background of the invention

In states of illness, surgical operations and injuries, profound changes are induced in the energy and protein metabolism of the human body. This means, for example, loss of active cellular mass, leading to muscular fatigue, pronounced apathy and loss of appetite, and a period of convalescence involving general weariness which, for instance after a biliary tract operation, may last 5-6 weeks before the patient has regained his normal function. The cellular mass which is broken down very rapidly in different states of illness will need a time for reestablishment which is about four times as long as the time of breakdown for the same mass.

In severe states of illness and injuries, and in postoperative states, parenteral nutritional support is generally applied. In the past, preparations for intraveneous nutritional support generally contained an aqueous solution of a high caloric content carbohydrate, such as glucose and the like, and electrolytes. In prolonged states of illness or in injuries and surgical operations, the nitrogen balance of the body must however be considered, i.e. the ratio of nitrogen loss to nitrogen intake. In the case of negative nitrogen balance, the parenteral nutritional support can be supplemented with amino acid supply

to improve the nitrogen balance. Different amino acid compositions for parenteral supply are previously known, see e.g. SE Patent Application 8203965-2 and DE-A 25 30 246 concerning amino acid nutrient compositions in renal failure, WO 82/00411 concerning a nutrient composition containing branched-chain amino acids, and WO 83/03969 concerning an aqueous nutrient solution consisting of L-amino acids.

The problem to be solved

From a survey made of the free amino acid pattern in the muscles, it has been found that skeletal muscle, which is the major body tissue in respect of weight, has a free amino acid pool, 62% of which consists of glutamine, see Bergström et al.: Intracellular free amino acid concentration in human muscle tissue, J. of Appl. Physiol., Vol 36, No 6, 1974. In states of illness, injuries or surgical operations, this content decreases by at least 50% and, in states of blood poisoning, even more, see Vinnars et al: Influence of the postoperative state on the intracellular free amino acids in human muscle tissue. Annals of Surg., Vol 182, 6:665-671, 1975.

It has been found that this glutamine reduction cannot be affected by enteral or parenteral nutritional support according to the methods hitherto available, see Vinnars et al.: Metabolic effects of four intravenous nutritional regiments in patients undergoing elective surgery. II. Muscle amino acids and energy rich phosphates. Clin. Nutr. 2:3-11, 1983. There probably is a correlation between the inability immediately postoperatively to make a negative nitrogen balance positive, the inability to normalise the exhausted intracellular glutamine pool, and the reduced muscular strength. This reduction probably depends on a reduced protein synthesis capacity posttraumatically in skeletal muscle, see Wernerman et al: Protein synthesis after trauma as studied by muscle ribosome profiles.

Proceedings in the 7th ESPEN Congress. Ed. Dietze et al, Karger, Basel.

The addition to the nutritional support of a dipeptide of the type ornithine-alpha-ketoglutarate to a commercial amino acid solution has been found to improve to some extent, whereas not to normalise the intracellular glutamine pool, see Leander et al: Nitrogen sparing effect of Ornicetil in the immediate postoperative state. Clin. Nutr. 4:43-51, 1985. This preparation is however very expensive, and it has not been possible so far to evaluate whether its use in parenteral nutrition confers a clinical advantage.

Postoperatively, the patient often exhibits loss of appetite, making it difficult to supply nutrition, although there are possibilities, by tube-feeding, of supplying different kinds of nutrient solutions. Since most patients do not tolerate this way of feeding, it becomes necessary to resort to intravenous feeding. The nutrition substrates available for energy metabolism are various sugar solutions and fatty emulsions, which today seem appropriate. However, the amino acid solutions available are inadequate, both because it is not possible to add tyrosine in sufficient amounts since this is a relatively insoluble amino acid, and because certain important amide derivatives of amino acids (glutamine and asparagine) cannot be included. This is due to difficulties in heat-sterilising solutions of such amides, and also to the fact that the amides are unstable when stored. Another problem is that these compounds are relatively sparingly soluble and therefore require large amounts of water when being prepared. This means that no commercial amino acid solutions for parenteral nutritional supply are available which contain the amino acid amides glutamine, its keto derivative alpha-ketoglutarate, asparagine or its ketoglutarate, acetoacetate.

Solution of the problem

After elective surgery, for instance biliary tract operations, it has been found that the negative nitrogen balance primarily depends on reduced protein synthesis which is assessed by determining the ribosome activity in skeletal muscle, see Wernerman et al: Protein synthesis in skeletal muscle after abdominal surgery: The effect of total parenteral nutrition. JPEN, 1985. An increased protein breakdown occurs only in very severe traumas and primarily in septic states. This reduced protein synthesis capacity cannot be affected by conventional intravenous or enteral nutritional support.

It has now been demonstrated for the first time that the addition of L-glutamine and/or alpha-ketoglutarate, and optionally L-asparagine, to a parenteral nutrition program can prevent such reduction of the protein synthesis capacity and, hence, also improve the nitrogen balance and even make it positive. The abnormal animo acid pattern intracellularly in skeletal muscle, and especially the 50% reduction of the glutamine pool involved, can then be partially prevented.

Preliminary tests on patients subjected to a biliary tract operation have shown that an addition of the amino acid amide L-glutamine or its keto derivative alpha-ketoglutarate, and optionally an addition of L-asparagine or its keto derivative, acetoacetate, to a conventional parenteral nutritional support program improves the nitrogen balance of the patients and hence also their recovery to a great extent. Besides, the pathological amino acid changes which normally occur after injury or surgical operation are normalised and, also, the reduction of the ribosome acitivity is prevented. Obviously, this is the first time it has been possible more specifically to act on the negative effects of injury or surgical operation on the protein metabolism.

It has thus been found that said vital amide derivatives can be brought into a form suitable for administration by sterile filtration of an aqueous solution, followed by rapid cooling and cold storage limited to a few months. One alternative is freeze-drying the sterile-filtered solution, yielding a sterile powder. Immediately before administration, this powder can be added to a conventional amino acid mixture. Also other forms of powder sterilisation, not relying on heat, are conceivable. The possibility of using the Na salt of the compounds in order to increase the solubility has also been considered.

The invention thus relates to a composition for therapeutic, especially postoperative and posttraumatic, parenteral nutritional support treatment, which composition is based on a conventional amino acid mixture, the composition comprising L-glutamine and/or alpha-ketoglutarate, and optionally L-asparagine and/or acetoacetate, the components of the composition, expressed in g dry component/l aqueous solution, being:

glycine	1-12
aspartate	1-10
glutamate	2-12
alanine	2-20
arginine	2-14
cysteine/cystine	0.4-2.0
histidine	2-8
isoleucine	2-8
leucine	2-8
lysine	2-12
methionine	1-6
phenylalanine	4-10
proline	4-10
serine	2-10
threonine	2-8
tryptophan	1-3
tyrosine	0.2-1
valine	2-8,

the composition being characterised in that it also contains 5-30 g/l L-glutamine and/or 5-25 g/l alpha-ketoglutarate, and optionally 0.5-10 g/l L-asparagine and optionally 0.5-10 g/l acetoacetate, or salts or esters thereof.

A preferred amount of L-glutamine in the composition of the present invention is 10-30 g/l and an especially preferred amount is 15-25 g/l, specifically 20 g/l. A preferred amount of alpha-ketoglutarate in the composition of the present invention is 10-25 g/l, specifically 16.5 g/l.

In therapeutic tests, preferred compositions have included the following suitable components (expressed in g dry component/l aqueous solution):

Example	1	2	3	4	5
glycine	5.9	5.9	5.9	5.9	5.9
aspartate	4.8	4.8	4.8	4.8	4.8
glutamate	6.8	6.8	6.8	6.8	6.8
alanine	12	12	12	12	12
arginine	8.4	8.4	8.4	8.4	8.4
cysteine/cystine	0.42	0.42	0.42	0.42	0.42
histidine	5.1	5.1	5.1	5.1	5.1
isoleucine	4.2	4.2	4.2	4.2	4.2
leucine	5.9	5.9	5.9	5.9	5.9
lysine	6.8	6.8	6.8	6.8	6.8
methionine	4.2	4.2	4.2	4.2	4.2
phenylalanine	5.9	5.9	5.9	5.9	5.9
proline	8.0	8.0	8.0	8.0	8.0
serine	6.0	6.0	6.0	6.0	6.0
threonine	4.2	4.2	4.2	4.2	4.2
tryptophan	1.4	1.4	1.4	1.4	1.4
tyrosine	0.4	0.4	0.4	0.4	0.4
valine	5.5	5.5	5.5	5.5	5.5
L-glutamine	20	-	10	10	10
alpha-ketoglutarate	-	16.5	10	10	10
asparagine	-	-	-	2	4
acetoacetate	-	-	-	2	-

When alpha-ketoglutarate should be included in the composition, it must be added in the form of its sodium salt or its esters, since it is otherwise extremely sparingly soluble. The glutamine can also be added in the form of the sodium salt thereof, thus improving its solubility.

The invention also relates to the use of L-glutamine and/or its derivative alpha-ketoglutarate and optionally L-asparagine and/or acetoacetate for the preparation of a composition intended for therapeutic, especially postoperative and posttraumatic, parenteral nutritional support treatment, which use is characterised in that L-glutamine and/or alpha-ketoglutarate and optionally L-asparagine and/or acetoacetate or salts or esters thereof, dissolved in water and sterile-filtered, are added in cold-stored and freeze-dried form or other sterile powder form to a commercial amino acid nutrient solution immediately before the therapeutic treatment.

<u>Implementation of the invention</u>

Commerical forms of L-glutamine, alpha-ketoglutarate and optionally L-asparagine and/or acetoacetate or salts or esters thereof are dissolved in sterile pyrogen-free water at 30-50°C. The solution is sterile-filtered and rapidly cooled and may thereafter be stored for a few months in a solution in a cooled state or for an even longer time in the frozen state, or stored after freeze-drying for several years in sterile powder form, until it should be used together with an amino acid solution of conventional commercial type, for instance of the Vamin® type (amino acid nutrient composition from KabiVitrum AB). Carbohydrates and fatty substances can also be added to the infusion solution. When using alpha-ketogutarate, this must be added in the form of its sodium salt or its esters, which is also possible, but not necessary, in the case of L-glutamine.

A newly prepared composition as above, either in large bags or in separate vials for each substrate, is then administered to patients exhibiting disordered nitrogen balance, resulting either from a surgical operation or from an injury or illness, the administration being conducted during a period of from 2-4 days to several weeks or until the patient can start eating ordinary food, with a dosage of 120-170 kJ/kg body weight/day, including 0.1-0.2 g amino acid nitrogen/kg body weight/day.

Example

15 voluntary patients subjected to a biliary tract operation but otherwise healthy, were divided into a test group of 6 persons and a control group of 9 persons. All patients were subjected to a parenteral nutritional support program with an intake of intravenous liquids of 35 ml/kg body weight/day (TPN), including 0.2 g amino acid nitrogen/kg body weight/day. This administration consisted of a balanced amino acid solution (Vamin®, KabiVitrum) having an amino acid composition in agreement with the first-mentioned 18 components in the preferred claimed composition, and also 135 kJ/kg body weight/day in the form of equal parts of fat (Intralipid, 20%, KabiVitrum) and carbohydrate (Glukos, 10%, Pharmacia Infusion). Supplementary electrolytes, tracer elements and vitamins were also administered. To the randomly selected test group was also administered 0.3 g/kg body weight/day of L-glutamine, while the control group did not receive this supplement.

Urine was collected continuously and analysed for urea content. On the basis hereof, it is possible to calculate the nitrogen balance, see MacKenzie et al, A simple method for estimating nitrogen balance in hospitalized patients: A review and supporting data for a previously proposed technique. J. Am.Col. Nutr. 4:575-581 (1985). In the control group, the nitrogen

balance was clearly negative each day during the measuring period of 3 days while, in the test group, it was statistically less negative, however with a substantial spread of the values for day 2. These values are given in the following Table as means ± deviation.

The protein synthesis in skeletal muscle was estimated by determining the total ribosome concentration and the percentage proportion of polyribosomes, see Wernerman et al: Size distribution of ribosomes in biopsy specimens of human skeletal muscle during starvation. Metabolism 34, 7:665-669, 1985. In the control group, an appreciable reduction of these values was obtained while, in the test group, they remained substantially unchanged after the surgery, see the following Table where the values relate to day 3.

TABLE

Data concerning patients and surgical operation as well as nitrogen balance and ribosome concentration

	Test group	Control group
Sex (male/female)	4/2	5/4
Age (years)	53 ± 6	58 ± 4
Length (cm)	168 ± 4	171 ± 4
Weight (kg)	69 ± 6	70 ± 4
Operation time (min)	102 ± 12	86 ± 15
Blood loss (ml)	180 ± 40	210 ± 30
Nitrogen balance		
Day 1	0.9 ± 0.8	-4.3 ± 1.0
Day 2	-2.5 ± 2.3	-3.7 ± 1.3
Day 3	-1.0 ± 1.3	-3.1 ± 0.9
Total ribosome concentration (OD/mg DNA*)		
Before surgery	40.0 ± 4.7	49.2 ± 5.6
After surgery	42.5 ± 3.5	37.5 ± 4.4
Percentage proportion of polyribosomes (%):		
Before surgery	52.3 + 2.7	50.6 ± 1.5
After surgery	53.2 ± 1.8	39.0 ± 3.3
Polyribosome concentration (OD/mg DNA*):		
Before surgery	20.9 ± 2.6	23.4 ± 2.9
After surgery	22.6 ± 1.9	14.5 ± 2.5

* Optical density units per mg tissue DNA

The intracellular concentration of glutamine in skeletal muscle was affected by the TPN program containing glutamine. The customary approximately 50% reduction postoperatively of the glutamine pool was partially prevented, and a significant minor reduction of the glutamine concentration could be observed. See Table below.

The glutamine concentration in mmole/l intracellular water in skeletal muscle prior to surgery and on the third postoperative day was as follows:

	Preoperatively	3rd postoperative day
Control group	24.65 ± 2.39	15.10 ± 1.28
Glutamine group	22.64 ± 1.82	17.70 ± 2.26

The above Tables show that the nitrogen balance and, thus, the postoperative recovery are favourably affected upon parenteral administration of the claimed composition as compared with the control group receiving a conventional composition. The Tables further show that the postoperative obligate reduction of the total ribosome concentration and the percentage proportion of polyribosomes could be prevented in the test group, and that the glutamine reduction in skeletal muscle was lower in the glutamine group.

In another similar study of patients who had been subjected to a biliary tract operation, the patients were divided into a test group of 8 persons and a control group of 9 persons. All patients were subjected to a parenteral nutritional treatment program (TPN) with an intake of intravenous liquids of 35 ml/kg body weight/day and an energy intake corresponding to 135 kJ/kg body weight/day in the form of equal parts of fat (Intralipid 20%, KabiVitrum) and carbohydrate (Glukos 10%, Pharmacia Infusion). The control group was given 0.2 g amino acid nitrogen/kg body weight/day in the form of Vamin® (KabiVitrum). The test group was also given 0.136 g alpha-ketoglutarate (α-KG)/kg body weight/day. Thus, both groups were given isonitrogenous and isocaloric amounts of amino acid and energy. Electrolytes, tracer metals and vitamins were administered to both groups.

The daily nitrogen balance in means ± SEM was as follows:

α-KG	-0.54±0.53	-1.65±1.86	-0.15±1.07	-2.33+1.30
Control	-3.64±0.64	-2.83±0.86	-3.16±0.70	-9.57±1.30
Significance	**(p<0.01)		*(p<0.05)	*(p<0.05)

The glutamine concentration (in mmole/kg wet weight) in skeletal muscle was affected in the following manner.

	Preoperatively	3rd postoperative day		Δ
α-KG	15.42±0.79	11.75±0.87	p<0.05	-3.67±0.49
Control	14.58±1.39	8.71±0.83		-5.87±0.91

The present amino acid nutrient compositions thus have a very favourable effect on postoperative and posttraumatic states since they provide an improved nitrogen balance and unaltered protein synthesis capacity and, hence, promote a considerably quicker and improved recovery of patients than is the case of previously known amino acid nutrient compositions.

CLAIMS

1. Composition for therapeutic, especially postoperative and posttraumatic, parenteral nutritional support treatment, which composition is based on a conventional amino acid mixture comprising the following components, expressed in g dry component g/l aqueous solution:

glycine	1-12
aspartate	1-10
glutamate	2-12
alanine	2-20
arginine	2-14
cysteine/cystine	0.4-2.0
histidine	2-8
isoleucine	2-8
leucine	2-8
lysine	2-12
methionine	1-6
phenylalanine	4-10
proline	4-10
serine	2-10
threonine	2-8
tryptophan	1-3
tyrosine	0.2-1
valine	2-8,

c h a r a c t e r i s e d in that the composition also contains 5-30 g/l L-glutamine and/or 5-25 g/l alpha-keto-glutarate, and optionally 0.5-10 g/l L-asparagine and optionally 0.5-10 g/l acetoacetate, or salts or esters thereof.

2. Composition as claimed in claim 1, c h a r a c t e r i s e d in that the amount of L-glutamine or salts or esters thereof is 10-30 g/l, preferably 20 g/l.

3. Composition as claimed in claim 1, characterised in that it contains 5-30 g/l L-glutamine, preferably 10-30g/l and 5-25 g/l alpha-ketoglutarate, preferably 10-25 g/l, and optionally 0.5-10 g/l L-asparagine and optionally 0.5-1 g/l acetoacetate or salts or esters thereof.

4. Composition as claimed in claim 1, characterised in that it contains 5-25, preferably 10-25 and most preferably 16.5 g/l alpha-ketoglutarate, and optionally 0.5-10 g/l L-asparagine and optionally 0.5-10 g/l acetoacetate or salts or esters thereof.

5. Composition as claimed in claim 1, 2, 3 or 4, characterised in that alpha-ketoglutarate is supplied in the form of the sodium salt thereof.

6. Composition as claimed in claim 1, 2 or 3, characterised in that L-glutamine is supplied in free acid form or in the form of the sodium salt thereof.

7. Method for preparing the composition as claimed in the preceding claims, characterised in that L-glutamine and/or alpha-ketoglutarate and optionally L-asparagine and optionally acetoacetate are dissolved in water and sterile-filtered and added, in cold-stored or freeze-dried form or other sterile powder form, to the conventional amino acid mixture immediately before the therapeutic treatment.

8. The use of the composition as claimed in any one of claims 1-6 for preparing a pharmaceutical preparation for therapeutic, especially postoperative and posttraumatic, parenteral nutritional support treatment.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE88/00578

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC 4

A 61 K 37/18, 31/195

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC 4	A 61 K 37/18, 31/195, 31/16
US Cl	514-561; 424-319, 320

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	WO, A1, 87/01589 (BRIGHAM AND WOMEN'S HOSPITAL) 26 March 1987 see claims 1, 5, 7 and 13, page 5, last paragraph - page 6, second paragraph, page 57, last paragraph - page 66 & EP, 0238553 JPT, 63501214	1-8
X	WO, A1, 87/03806 (VEECH RICHARD L) 2 July 1987 see claims, pages 20-21, page 26, last paragraph, pages 29-31 & EP, 0250559	1-8
X	EP, A3, 0 146 474 (SYNTHELABO) 26 June 1985 see claim 7, page 2, line 28 - page 3, line 19, page 3, lines 31-34 & FR, 2556593 JP, 60227656 OA, 7904 AU, 564922	1-8

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1988-12-16	1989 -01- 16
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Gerd Wranne Gerd Wranne

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	EP, A1, 0 046 167 (LENTIA GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG) 24 February 1982	1-8